Phase Ib/II of efficacy and safety of CAPOX regimen combined with sindilizumab and bevacizumab in the first-line treatment of recurrent or metastatic adenocarcinoma of the stomach and gastroesophageal junction Informed consent form for clinical Research

2022-08-31

Dear subject

We invite you to participate in the research of "Phase Ib/II Clinical Study on the Efficacy and Safety of CAPOX Regimen Combined with Cindilizumab and Bevacizumab in the First Line Treatment of Recurrent or Metastatic Gastric and Gastroesophageal Junction Adenocarcinoma". This study will be conducted in west china hospital Hospital, and it is estimated that 57 subjects will participate voluntarily. This research has been reviewed and approved by the Biomedical Ethics Review Committee of west china hospital.

1.Why do you want to carry out this research?

Disease burden and treatment status

Every year, there are millions of new cases of gastric cancer in the world, accounting for about 40% in China, and the morbidity and mortality rate rank among the top three malignant tumors in China. About 70% of gastric cancer patients in China are in the advanced stage when they are diagnosed, and even patients undergoing radical surgery often have recurrence and metastasis, which undoubtedly makes it difficult to treat gastric cancer. Although the chemotherapy regimen for advanced gastric cancer has been progressing in recent years, the first-line chemotherapy for advanced gastric cancer is still not effective, and the median survival

time hovers around one year. Chemotherapy is still facing a bottleneck in the treatment of advanced gastric cancer. In recent years, monoclonal antibody against programmed cell death protein 1 PD-1 has attracted wide attention as a new type of immunotherapy, and many large-scale global multicenter clinical studies have been carried out in patients with gastric cancer, and gratifying results have been achieved. Therefore, in 2021, the CSCO gastric cancer expert guide of China Society of Clinical Oncology added the recommendation that PD-L1 CPS≥5 be given to patients with advanced gastric cancer by XELOX/FOLFOX regimen chemotherapy combined with PD-1 monoclonal antibody as the first-line treatment. However, the curative effect of combined therapy is still limited, and the patients with low expression of PD-L1 have no obvious benefit. Bevacizumab can effectively start and activate T cells by inhibiting VEGF-mediated DC cell maturation disorder. At the same time, bevacizumab can normalize tumor blood vessels and increase T cell infiltration in tumors. Theoretically, bevacizumab combined with anti-PD-L1/PD-1 immunotherapy can completely encircle tumor cells. At present, this theory has been verified in many malignant tumors such as liver cancer, kidney cancer, non-small cell lung cancer, etc., and has become the standard treatment mode. Therefore, the regimen of chemotherapy combined with PD-1 monoclonal antibody combined with bevacizumab may further improve the therapeutic effect and prolong the survival time of patients with advanced gastric cancer. Dilizumab Sintilimab is a recombinant human immunoglobulin 4(IgG4) type anti-PD-1 monoclonal antibody injection independently developed by Cinda Biopharmaceutical (Suzhou) Co., Ltd. Its anti-tumor activity and safety have been confirmed in many clinical studies, and it has been approved by SFDA in china food and drug administration, China. In addition, phase III clinical studies have preliminarily verified the effectiveness of the combination of this drug and chemotherapy in patients with advanced gastric cancer. Bevacizumab (Dayutong) is also an anti-VEGF monoclonal antibody independently developed by Cinda Biopharmaceutical (Suzhou) Co., Ltd., and approved by SFDA for listing.

This experiment hopes to explore the safety and efficacy of XELOX regimen combined with PD-1 monoclonal antibody (sindilizumab) combined with bevacizumab (Dayutong) in the first-line treatment of unresectable adenocarcinoma of stomach and gastroesophageal junction, and look forward to better serving patients.

B. The purpose of this study

This experiment hopes to explore the safety and efficacy of XELOX regimen combined with PD-1 monoclonal antibody (sindilizumab) and bevacizumab (Dayutong) in the first-line treatment of unresectable adenocarcinoma of stomach and gastroesophageal junction, and to prolong the disease-free time of patients. I look forward to serving patients better. This research project has been approved by the ethics committee of your doctor's medical center.

C. research participants and the number of participants expected to be included in the study

This study was conducted in west china hospital, and it is expected that 57 patients with unresectable adenocarcinoma of stomach and gastroesophageal junction will be included.

If you agree to participate in the study, you will be treated with the following regimen:

Standard XELOX regimen combined with sindilimab and bevacizumab, once every 3 weeks. Evaluate the curative effect after 2 times of treatment, and decide the next treatment plan. If it is still effective after 4-6 cycles, the maintenance treatment combined with sindilimab and bevacizumab will continue until you are not suitable or ineffective.

Blood / tissue samples were collected before, during and after treatment for biomarkers and gene analysis.

What do you need to do if you participate in the study?

a. Before you are enrolled in the study, you will be examined to determine if you are eligible for the study.The doctor will ask and record your medical history and give you a physical examination. You need to do: enhanced CT or / and MRI;CEA and carbohydrate antigen were detected;Physical and chemical tests such as blood routine, urine routine, liver and kidney function, blood electrolyte, etc;ECG;The ECoG and QOL scores of physical state were compared.All of the above examinations are necessary to judge the condition of the disease and whether it can be treated, which conforms to the clinical routine and belongs to the scope of national medical insurance reimbursement, without additional burden on patients.Biomarker detection is a free project.

You are a qualified participant. You can participate in the study voluntarily and sign the informed consent form.

If you do not want to participate in the study, we will treat you as you wish.

b. If you volunteer to participate in the study, and after completing the pre-treatment examination, the specialist judges that you can not be surgically removed, the following steps will be followed for the study (detailed description of treatment and inspection items according to the follow-up time point).

- Treatment observation will continue until disease progression or intolerable toxicity occurs.
- Within one week before the beginning of each treatment cycle: you should go to the hospital to check the weight, blood routine, urine routine, liver and kidney function, blood electrolyte, etc;ECoG score;CTCAE score of common adverse events;QOL survey.
- The curative effect was evaluated every 6-8 weeks. The patients were followed up by telephone during discharge.
- One or two blood samples of biomarkers will be collected in the middle of treatment.
- According to the doctor's arrangement, routine reexamination and curative effect evaluation test were carried out.

After treatment: you should go to the hospital for CT or / and MRI examination, weight, tumor markers, carcinoembryonic antigen and carbohydrate antigen detection, blood routine, urine routine, liver and kidney function, blood electrolyte and other physical and chemical tests;ECG;ECoG and QOL scores;And biomarker blood samples.

c. Other matters that need your cooperation. Your follow-up is very important. You must take the outpatient records with you according to the follow-up time agreed by the doctor and you (during the follow-up stage, the doctor may know your situation by telephone or visiting the door).Your follow-up is very important because the doctor will judge whether the treatment you receive is really effective and guide you in time.

You must take the medicine according to the doctor's guidance, and please fill in your medication record timely and objectively, and bring other drugs you are taking, including those that you need to continue to take if you have other complicated diseases.

If you need other treatment, please contact your doctor in advance.

3. What are the alternative treatment options?

If you do not participate in this study, your doctor will choose other treatments for you, such as standard first-line chemotherapy, or chemotherapy combined with PD-1 monoclonal antibody. Your doctor will explain the advantages and disadvantages of all the alternative treatments, and you can decide whether to participate in the study.

4. Who are not suitable for the study?

1) Patients who are participating in other clinical trials;2) The researchers believe that other reasons are not suitable for clinical trials.

In addition, patients who meet one of the following conditions are not allowed to participate in this study:

- HER2 is known to be positive
- Gastric cancer known as squamous cell carcinoma, undifferentiated or other tissue types, or adenocarcinoma mixed with other tissue types
- There are uncontrolled or symptomatic active central nervous system (CNS) metastases, which can be characterized by clinical symptoms, brain edema, spinal cord compression, cancer metastasis, malignant meningitis, leptomeningeal disease, and / or progressive growth.Patients with CNS metastases can be enrolled in the study if they are adequately treated and their psychiatric symptoms can return to baseline level at least 2 weeks before randomization (except for residual signs or symptoms related to CNS treatment).In addition, subjects were required to discontinue corticosteroids or receive prednisone (or equivalent other corticosteroids) at least 2 weeks before randomization, or to receive a stable or gradually reduced dose of prednisone (or equivalent) at least 2 weeks before randomization
- There were hydrothorax and ascites which could not be controlled by puncture and drainage within 14 days before the random;Pericardial effusion with clinical symptoms or moderate or above
- The weight of the subjects decreased by more than 20% in the first two months of randomization
- The following treatments or drugs were received before randomization: a) major surgery was performed within 28 days before randomization (tissue biopsy and peripherally inserted central catheter operation PICC for diagnosis are allowed; b) immunosuppressive drugs were used within 7 days before randomization,Does not include nasal and inhaled corticosteroids or physiological doses of systemic hormones (i.e. no more than 10 mg / D of nisone or other corticosteroids with equivalent physiologic doses);c) Live attenuated vaccine was administered within 28 days before randomization or within 60 days after the end of drug treatment;d) Antineoplastic therapy (including chemotherapy, radiotherapy, immunotherapy, endocrine therapy, targeted therapy, biotherapy or tumor embolization) within 28 days before randomization
- Any other malignant tumor was diagnosed within 3 years before entering the study, except basal cell carcinoma of skin or squamous or superficial bladder

cancer, carcinoma in situ of cervix, intraductal carcinoma of breast and papillary thyroid carcinoma that can be treated locally and cured.

- There is any active, known or suspected autoimmune disease.Subjects who were in a stable state and did not need systemic immunosuppressive therapy were allowed to be included, such as type I diabetes mellitus, hypothyroid diabetes mellitus requiring hormone replacement therapy only, and skin diseases without systemic treatment (e.g., vitiligo, psoriasis and alopecia)
- Previously received anti-PD-1 / PD-L1 antibody, anti-CTLA-4 antibody or other drugs acting on T-cell co stimulation or examination cell co stimulation or checkpoint pathway
- There were significant bleeding symptoms or bleeding tendency in 3 months before random;Gastrointestinal perforation and / or gastrointestinal fistula occurred within 6 months before randomization;Arteriovenous thrombosis events occurred in the first 6 months, such as cerebrovascular accident (including transient ischemic attack, cerebral hemorrhage, cerebral infarction), deep vein thrombosis and pulmonary embolism, etc
- Major vascular disease (e.g. aortic aneurysm requiring surgical repair or recent peripheral artery thrombosis) within 6 months before the start of study treatment
- Severe, unhealed or dehiscent wounds and active ulcers or untreated fractures
- There were peripheral neuropathy > 1 grade
- Clinical signs or symptoms of intestinal obstruction and / or gastrointestinal obstruction, including incomplete obstruction related to the original disease requiring routine parenteral hydration, parenteral nutrition, or tube feeding within 6 months prior to the initiation of study treatment: at the initial diagnosis, if the patient with incomplete obstruction / obstruction syndrome / intestinal obstruction signs / symptoms received definite (surgical) treatment to resolve the symptoms,Patients may be admitted to the study
- Interstitial lung disease, non infectious inflammation or uncontrollable systemic diseases (such as diabetes, hypertension, pulmonary fibrosis and acute pneumonia, etc.)
- It is known that it is allergic to the study drug or any auxiliary materials, or it has had a serious allergic reaction to other monoclonal antibodies.
- Human immunodeficiency virus (HIV) infection or known acquired immunodeficiency syndrome (AIDS)
- Untreated active hepatitis B is defined as HBV-DNA $\geqslant$ 500 IU/ml; Hepatitis C, defined as HCV-RNA higher than the detection limit of analytical methods; Or co-infection of hepatitis B and C.
- In the first 6 months, the following conditions occurred randomly: myocardial infarction, severe/unstable angina pectoris, NYHA2 or above cardiac insufficiency, clinically significant supraventricular or ventricular arrhythmia and symptomatic congestive heart failure
- Poor control of antihypertensive drugs (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg)

- Systemic antibiotic use ≥7 days in the first 4 weeks at random, or unexplained fever > 38.5° C during the screening period/before the first dose (fever caused by tumor can be included in the group as judged by the researcher).
- Known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation
- Have participated in any other drug clinical study within the first 4 weeks at random, or have no more than 5 half-lives from the last drug study.
- Have a known history of psychotropic substance abuse or drug abuse
- There are other serious physical or mental disorders with abnormal laboratory examination, which may increase the risk of participating in the study, or interfere with the results of the study and the patients that the researchers think are not suitable for participating in the study.

5. What are the risks of participating in research?

The common side effects of chemotherapy drugs in this study are nausea, vomiting, bone marrow suppression (decrease of white blood cells, granulocytes and platelets) and damage of liver and kidney function. Oxaliplatin may also have non-neurotoxic side effects such as allergic reaction, diarrhea, stomatitis, skin toxicity and neurotoxic effects such as paresthesia, dullness and even pain. The most common adverse events involved in PD-1 monoclonal antibody therapy include: skin mucosal toxicity, colitis and diarrhea, hepatotoxicity, endocrine adverse reactions; Other organs, such as thyroid, lung, kidney, eyes, nerves, blood, etc., may have immunotherapy-related toxicity, and few patients may have serious immunotherapy-related adverse reactions.

Bevacizumab used in this study is over-indicated. The common side effects are hypertension, proteinuria, renal dysfunction, gastrointestinal perforation, bleeding, etc. The uncommon side effects are arterial thromboembolism, reversible posterior leukoencephalopathy syndrome, etc. The above side effects may also occur in this study.

If any discomfort occurs, you should inform your doctor, and the researcher will take active prevention and timely treatment according to the situation, and decide whether to stop the drug or reduce it. During the study period, you need to go to the hospital for follow-up, and do some hematological and imaging examinations in order to evaluate the adverse reactions and therapeutic effects. These are routine examination items required to judge your condition in clinical treatment. This study does not increase your examination cost and burden.

This study will buy insurance for clinical trial research for you to pay for the claims. In case of research-related damages, you will be given active and free treatment and reasonable compensation, so that your personal safety will be more secure.

6. What are the possible benefits of participating in research?

By taking part in this research, your condition may be improved, and this research will also help to determine which treatment method can treat other patients with similar conditions more safely and effectively.

We hope whatever treatment you receive will help you. Clinical research and clinical practice show that PD-1 combined with chemotherapy is effective in the first-line treatment of gastric cancer, and it is the standard first-line treatment scheme for patients with unresectable gastric cancer and adenocarcinoma of gastroesophageal junction. If combined with bevacizumab, the curative effect may be further improved, but all anti-tumor treatments are only effective for some patients. We can't guarantee that they are definitely effective, and you may not benefit from this study. The information in this study may help us to add new treatments for gastric cancer.

In this study, you will have a careful discussion, evaluation and monitoring of your condition by the gastric cancer team in the Department of Abdominal Oncology of West China Hospital (including experts in radiation oncology, oncology, tumor intervention and targeted immunotherapy). Your quality of life and tolerance to treatment may be improved. Or the research doctor in charge will provide free outpatient follow-up and consultation at any time at least once a week, and will closely observe and deal with adverse reactions. If the treatment doesn't work, you can ask your doctor about possible alternative treatments.

7.Do I have to pay for the study?

This study is a type of clinical research initiated by researchers. The chemotherapy involved in this study is reimbursed in the national medical insurance catalogue, and the anti-PD-1 monoclonal antibodies-sindilizumab and bevacizumab-Dayou involved in this study are provided by Cinda Pharmaceutical. Your PD-1 monoclonal antibody and bevacizumab are free of charge.

The examinations involved in the study are also medical treatment items reimbursed by provincial, municipal and regional medical insurance, in order to evaluate adverse reactions and therapeutic effects. These are routine examination items required to judge your condition in clinical treatment, and do not increase your financial burden. You will also be paid for participating in this research. Subjects in Chengdu will receive 50 yuan transportation subsidy, and subjects outside Chengdu will receive 100 yuan transportation subsidy. If all subjects conduct group pharmacokinetic study, they will receive a 50 yuan subsidy once. In this study, free specialist clinics will be provided during the study period and within 2 years after the end of the study to compensate the transportation follow-up subsidy of the subjects during the study period. The treatment and examination for other diseases that you have combined at the same time will not be included in the free scope.

8. Is personal information confidential?

Your research materials will be kept in west china hospital, and your medical records can be consulted by researchers, research authorities and ethics review committee. Any public report on the results of this research will not disclose your personal identity. We will make every effort to protect the privacy and personal information of your personal medical data within the scope permitted by law.

9.

Do I have to take part in the research?

Participation in this study is completely voluntary. You can refuse to participate in the study, or withdraw from this study at any time at any stage of the experiment without discrimination and retaliation, and your medical treatment and rights will not be affected. If you decide to withdraw from this study, please contact your doctor for proper diagnosis and treatment of the disease.

Subject Statement: I have read the above introduction of this research, and my researchers

have fully explained and explained the purpose, operation process, possible risks and potential benefits of participating in this research, and answered all my related questions. Volunteer to participate in this research.

I agree ☐ or refuse ☐ to use my research data and biological specimens for other research except this research.

Name of the subject:: _____

Signature of the subject: _____ Date: __ __ __ __

Contact telephone number of the subject: _____

Contact telephone number of the subject: mobile phone number:

Name of legal representative in block letters: (if applicable)
Relationship with subjects:

Signature of legal representative: Date _____
Reasons for signature by legal representative:

Name of witness in block letters: (if applicable)
Signature of witness: Date _____
Reasons for needing witness's signature:

Doctor's statement: I have explained the details of this study to the above-mentioned volunteer, and provided him/her with an original signed informed consent form. I confirm that I have explained the situation of this research to the subjects in detail, especially the ethical principles and requirements such as risks and benefits, free and compensation, damages and compensation, voluntariness and confidentiality that may arise from participating in this research.

Doctor's signature: Date: _____ Date:

Doctor's contact number: _____

West china hospital Biomedical Ethics Review Committee Tel: 028-85422654,028-85423237